REMARKS

Reconsideration of this application is requested in view of the proposed amendments to the claims and the remarks presented herein. Entry of the amendment is requested under the provisions of Rule 116 as it puts the application in condition for allowance or in better condition for appeal.

The claims in the application are claims 22 to 34, all other claims having been cancelled.

The Examiner has indicated that there is no support in the specification for the expression "conjugate equine estrogen" and "estrogenic deficiencies" and this is an incorrect statement since it is clear from page 4, line 10 that the expression "equine conjugated estrogens" is supported in the specification as filed. With respect to the Examiner's statement that the term is not well known, Applicatns are submitting herewith, in addition to the material already submitted, a number of articles from the literature showing that the expression "conjugated equine estrogen" is an art recognized term. There are a number of references set forth in the literature which unequivocally demonstrates that this is a well known term in the art. If the Examiner is going to maintain the rejection, the Examiner should indicate some basis for maintaining the same since Applicants have unequivocally proven that the term is a well known art term.

All of the claims were rejected under 35 USC 103 as being obvious over the Conrad et al reference. The Examiner states that Conrad et al teaches the sequential combination of oral estrogen estradiol and nomegenstrol acetate progesterone component at 1.5 to 3.75 mg per unit dose and the treatments are stated to be useful for estrogen deficiency which significantly reduces menopausal complaints. The Examiner deems that the claims differ from the reference in having different generic scope but the method would be obvious to one skilled in the art.

Applicants respectfully traverse this ground of rejection since the Conrad et al reference does not render obvious Applicants' invention. Applicants will concede that Conrad et al relates to a sequential hormonal combination wherein it is made up of dosage units comprising only estrogen, then dosage units comprising a combination of estrogen and a progesterone and then dosage units comprising only a placebo. As pointed out on page 5 of the last response, the amount of estradiol combined with nomegensterol acetate is only administered for 14 consecutive days after which, estradiol alone is administered for 10 consecutive days followed by administration of a placebo for the last 7 days. One of the drawbacks of this type of treatment is to create artificial menstrual cycles that are followed by bleeding. This therapeutic scheme for women for whom the menopause is recent but is not always well accepted in the long term which in part explains the poor observance of the treatment.

In contrast thereto, the claimed method has for its purposes to realize a replacement treatment for the menopause which cures the climateric symptomology and prevents osteoporosis and the onset of illnesses which does not create artificial cycles such as Conrad et al followed by withdrawal bleeding. In contrast to the trisequential replacement of hormonal treatment of Conrad et al, the present invention avoids menopausal women from having periods which generally are not desired by women having menopause of whom lasting well in the past such as women 60 to 70 years of age. Moreover, the Conrad et al studies are not directed to the effect of an estradiol/progesterone combination but, rather, the effect of the latter in an entire sequential combination. The sequential Conrad et al therapeutic effect is a result of first, the hormonal effect of 17ß-estradiol alone followed by the hormonal effect of the estrogen-progestogen combination of 17ß-estradiol and nomegestrol acetate and finally, the non-effect of the placebo. This effect cannot be considered as a simple combination of each presumed effect of each part of the combination. Moreover, the hormonal effect of 17ß-estradiol alone is <u>distinct</u> from the treatment of estrogens-progestogen combination. Therefore, Applicants' method and the advantages thereof would in no way be taught by the Conrad et al reference which merely has a trisequential treatment. Therefore, withdrawal of this ground of rejection is requested.

All of the claims were rejected under 35 USC 103 as being

obvious over the Fraser et al reference and the Cano et al reference. The Examiner states that both references teach the use of oral estradiol-progesterone combination and that Cano et al teaches estradiol-progesterone combination for cardiovascular diseases and discloses it as being a good alternative in post menopausal replacement therapy. According to the Examiner, Fraser et al teaches the effects of the addition of nomegestrol acetate in post-menopausal treatment in addition to estrogen to prevent endometrial abnormalities. The Examiner deems that the claimed method would be obvious therefrom.

Applicants respectfully traverse these grounds of rejection since the two references would in no way teach Applicants' invention. The Fraser et al reference relates to the effects of the addition of nomegestrol acetate to post-menopausal estrogen therapy and in this study, estradiol is orally administered to women and patients who took nomegestrol acetate by the implant administration method at regular intervals for 12 days and the women showed a regular progesterone induced withdrawal bleeding each month. The Cano et al reference relates to the effect of estrogen-progestative combination of plasma lipids and lipoproteins but this administration is continuous and the progestational compound is madroxyprogesterone.

In Applicants' method, the progesterone and the estrogen are orally administered for 21 to 25 days per month and this treatment

is intended to prevent the appearance of withdrawal bleeding. Therefore, neither reference anticipates or renders obvious Applicants' invention and withdrawal of these grounds of rejection is requested.

All of the claims were rejected under 35 USC 103 as being obvious over the Lanquetin et al patent which, according to the Examiner teaches treating estrogen deficiencies in menopausal women by oral administration of an estrogen alone followed by the combination of estrogen-progesterone combination and then a placebo.

Applicants respectfully traverse this ground of rejection since the Lanquetin et al patent in no way anticipates or renders obvious Applicants' invention and is the scientific work of Conrad et al which again, teaches a trisequential administration rather than Applicants' claimed method of administration and the arguments against Conrad et al apply also to Lanquetin et al. Therefore, the reference in no way anticipates or renders obvious Applicants' invention and withdrawal of this ground of rejection is requested.

In view of the proposed amendments tot he claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application of the application is requested.

Respectfully submitted,
Bierman, Muserlian and Lucas

By: 
Charles A. Muserlian #19,683
Attorney for Applicants
Tel.# (212) 661-8000

CAM:ds
Enclosures

1/13 PASCAL - (C) CNRS
NO : PASCAL 96-0212733 INIST
ET : A comparative study of safety and efficacy of continuous low dose oestradiol released from a vaginal ring compared with **conjugated** **equine** **oestrogen** vaginal cream in the treatment of postmenopausal urogenital atrophy
AU : AYTON RA; DARLING GM; MURKIES AL; FARRELL EA; WEISBERG E; SELINUS I; FRASER IS
AF : Menopause Service, Division of Gynaecology, Royal Women's Hospital/Melbourne/AUS
DT : Periodique; LA
SO : British journal of obstetrics and gynaecology; ISSN 0306-5456; Coden BJOGAS; GBR; DA. 1996; VOL. 103; NO. 4; PP. 351-358; BIBL. 17 ref.
LA : ENG
EA : Objective To compare the safety, efficacy and acceptability of a continuous low dose oestradiol releasing vaginal ring with conjugated equine oestrogen vaginal cream in the treatment of postmenopausal urogenital atrophy. Design An open, parallel, comparative multicentre trial. Setting Sydney and Melbourne, Australia. Participants and Interventions One hundred and ninety-four postmenopausal women with symptoms and signs of urogenital atrophy were randomised on a 2 :1 basis to 12 weeks of treatment with an oestrogen vaginal ring versus an oestrogen cream. Main outcome measures and results Equivalence (95 % CI) was demonstrated between the two treatments for relief of vaginal dryness and dyspareunia, resolution of atrophic signs, improvement in vaginal mucosal maturation indices and reduction in vaginal pH. No significant difference was demonstrated in endometrial response to a progestogen challenge test and equivalence was demonstrated in the incidence of intercurrent bleeding episodes. The vaginal ring was significantly more acceptable than the cream (P < 0.0001), and was preferred to the cream (P < 0.001). Conclusion With equivalent efficacy and safety and superior acceptability to vaginal cream, the low dose oestradiol vaginal ring is an advance in vaginal delivery systems for the treatment of urogenital atrophy.
CC : C02B20H
FD : Atrophie; Appareil génital femelle; Appareil urinaire; Postménopause;
LO : INIST-1096.354000044565710120

2/13 PASCAL - (C) CNRS
NO : PASCAL-M 89-0140344
ET : Effects of **conjugated** **equine** **oestrogen** with and without the addition of cyclical norgestrel on serum and urine electrolytes, and the biochemical indices of bone metabolism and liver function
AU : FLETCHER CD; FARISH E; DAGEN MY; ALLAM BF; HART DM
AF : Stobhill gen. hosp., dep. biochemistry/Glasgow G21/GBR
DT : Periodique; LA
SO : Maturitas; ISSN 0378-5122; Coden MATUDK; NLD; DA. 1988; VOL. 9; NO. 4; PP. 347-357; BIBL. 42 ref.
LA : ENG
CC : C02B02P
LO : CNRS-18011

3/13 PASCAL - (C) CNRS
NO : PASCAL-M 87-0289618
ET : The effects of **conjugated** **equine** **oestrogens** with and without a cyclical progestogen on lipoproteins, and HDL subfractions in postmenopausal women

AU : FARISH E; FLETCHER CD; HART DM; TEO C; ALAZZAWI F; HOWIE C
AF : Stobhill gen. hosp./Glasgow G21/GBR
DT : Periodique; LA
SO : Acta endocrinologica (Kobenhavn); ISSN 0001-5598; DNK; DA. 1986; VOL. 113; NO. 1; PP. 123-127; BIBL. 30 ref.
LA : ENG
CC : 002B020
LO : CNRS-5321

4/13 PASCAL - (C) CNRS
NO : PASCAL-M 85-C039522
ET : A new combination of **conjugated** **equine** **oestrogens** and medroxy-progesterone for treatment of climateric complaints
AU : CULLBERG G; KNUTSSON F; MATTSSON LA
AF : Univ. Goeteborg, dep. obstetrics gynaecology/Goeteborg 41685/SWE
DT : Periodique; LA
SO : Maturitas; ISSN 0378-5122; NLD; DA. 1984; VOL. 6; NO. 1; PP. 55-63; BIBL. 17 ref.
LA : ENG
CC : 002B02P
LO : CNRS-18011

5/13 PASCAL - (C) CNRS
NO : PASCAL 83-X-0242416
ET : EFFECTS OF INTRAVAGINAL **OESTROGEN** TREATEMENT UPON THE VAGINAL ABSORPTION OF **CONJUGATED** **EQUINE** **OESTROGENS**
AU : CARLSTROEM K; KARLGREN E; FURUHJELM M; RYD KJELLEN E
AF : HUDDINGE UNIV. HOSP./HUDDINGE 14186/SWE
DT : PERIODIQUE;LA
SO : MATURITAS; ISSN 0378-5122; NLD; DA. 1982; VOL. 4; NO 4; PP. 277-283; BIBL. 19 REF.
LA : ENG
CC : 361B04E
LO : CNRS-18011

6/13 PASCAL - (C) CNRS
NO : PASCAL 82-X-0322397
ET : DOSE-RELATED CHANGES IN VAGINAL CYTOLOGY AFTER TOPICAL **CONJUGATED** **EQUINE** **OESTROGENS**
AU : DYER GT; YOUNG O; TOWNSEND PT; COLLINS WP; WHITEHEAD MI; JELOWITZ J
AF : KING'S COLL. HOSP. MED. SCH./LONDON SE5 8RX/GBR
DT : PERIODIQUE;LA
SO : BR. MED. J.; ISSN 0007-1447; GBR; DA. 1982; VOL. 284; NO 6318; PP. 739; BIBL. 5 REF.
LA : ENG
CC : 361A05F
LO : CNRS-5002

7/13 PASCAL - (C) CNRS
NO : PASCAL 82-X-0159758
ET : **CONJUGATED** **EQUINE** **OESTROGEN** VERSUS PLACEBO IN THE MANAGEMENT OF MENOPAUSAL SYMPTOMS
AU : HALLES JD; NELSON JB; SCHNEIDER M; RENNIE GC; BURGER HG
AF : PRINCE HENRY'S HOSP./MELBOURNE VICTORIA 3004/AUS
DT : PERIODIQUE;LA
SO : MED. J. AUST.; ISSN 0025-729X; AUS; DA. 1981; VOL. 2; NO 7; PP. 340-342; 2 P.; BIBL. 9 REF.
LA : ENG
CC : 361A05F
LO : CNRS-3557

8/13 PASCAL - (C) CNRS
NO : PASCAL 80-X-0322564
ET : PLASMA EQUILIN CONCENTRATIONS IN AN OOPHORECTOMIZED WOMAN FOLLOWING INGESTION OF **CONJUGATED** **EQUINE** **OESTROGENS** (PREMARIN)
AU : MORGAN MRA; WHITTAKER PG; DEAN PDG; LENTON EA; SEXTON L; COOKE ID
AF : UNIV. LIVERPOOL, DEP. BIOCHEM.,GBR

DT : PERIODIQUE;LA
SO : EUROP. J. CLIN. INVEST.; GBR; DA. 1979; VOL. 9; NO 6; PP. 473-474; BIBL. 7 REF.
LA : ENG
CC : 361A05F
LO : CNRS-5809

9/13 PASCAL - (C) CNRS
NO : PASCAL 80-5-0371978
ET : A RADIOIMMUNOASSAY FOR EQUILIN IN POST-MENOPAUSAL PLASMA: PLASMA LEVELS OF EQUILIN DETERMINED AFTER ORAL ADMINISTRATION OF **CONJUGATED** **EQUINE** **OESTROGENS** (PREMARIN)
AU : MORGAN MRA; WHITTAKER PG; FULLER BP; DEAN PDG
AF : UNIV. LIVERPOOL, DEP. BIOCHEM.,LIVERPOOL L69 3BX,GBR
DT : PERIODIQUE;LA
SO : J. STEROID BIOCHEM.; GBR; DA. 1980; VOL. 13; NO 5; PP. 551-555; BIBL. 16 REF.
LA : ENG
CC : 361A05F
LO : CNRS-14629

10/13 PASCAL - (C) CNRS
NO : PASCAL 80-5-0256633
ET : SERUM EQUILIN, OESTRONE, AND OESTRADIOL LEVELS IN POSTMENOPAUSAL WOMEN RECEIVING **CONJUGATED** **EQUINE** **OESTROGENS** (PREMARIN')
AU : WHITTAKER PG; MORGAN MRA; DEAN PDG; CAMERON EHD; LIND T
AF : UNIV. LIVERPOOL, DEP. BIOCHEM.,LIVERPOOL L69 3BX,GBR
DT : PERIODIQUE;LA
SO : LANCET; GBR; DA. 1980; NO 8158; PP. 14-16; BIBL. 14 REF.
LA : ENG
CC : 361A05F
LO : CNRS-5004

11/13 PASCAL - (C) CNRS
NO : PASCAL 79-5-0264753
ET : PLASMA LEVELS OF OESTRONE, OESTRADIOL AND GONADOTROPHINS IN POSTMENOPAUSAL WOMEN AFTER ORAL AND VAGINAL ADMINISTRATION OF **CONJUGATED** **EQUINE** **OESTROGENS** (PREMARIN)
AU : ENGLUND DE; JOHANSSON EDB
AF : UNIV. HOSP., UPPSALA, SWE
DT : PERIODIQUE;LA
SO : BRIT. J. OBSTETR. GYNAECOL.; GBR; DA. 1978; VOL. 85; NO 12; PP. 957-964; BIBL. 24 REF.
LA : ENG
FA : ON OBSERVE UNE AUGMENTATION MARQUEE DES TAUX D'OESTRONE PLASMATIQUE ET 24 HEURES APRES TRAITEMENT LES TAUX SONT AU DESSUS DE CEUX DE LA PHASE FOLLICULAIRE. L'ELEVATION D'OESTRADIOL EST MOINS NETTE. L'ACTIVITE BIOLOGIQUE DU PREMARIN EST IDENTIQUE PAR VOIE ORALE ET INTRA VAGINALE
LO : CNRS-1086

12/13 PASCAL - (C) CNRS
NO : PASCAL 75-351-11581
ET : (COMPARAISON DES EFFETS DE L'ETHINYL OESTRADIOL ET DES OESTROGENES EQUINS CONJUGUES CHEZ DES FEMMES CASTREES)
ET : COMPARISON OF THE EFFECTS OF ETHINYL OESTRADIOL AND **CONJUGATED** **EQUINE** **OESTROGENS** IN OOPHORECTOMIZED WOMEN
AU : BOLTON CH; ELLWOOD M; HARTOG M; MARTIN R; ROWE AS; WENSLEY RT
AF : DEP. MED., UNIV. BRISTOL, BRISTOL
DT : PERIODIQUE;LA
SO : CLIN. ENDOCRINOL.; G.B.; DA. 1975; VOL. 4; NO 2; PP. 131-138; BIBL. 1P.1/2
LA : ENG
FA : TRAITEMENT QUOTIDIEN AVEC L'ETHINYL OESTRADIOL (20 OU 50 MU G) OU LA PREMARINE (0,625 ET 1,25MG). AUCUN EFFET SUR LE CHOLESTEROL SERIQUE, LA DUREE DE LYSE DU CAILLOT, LE FIBRINOGENE PLASMATIQUE, L'ADHERENCE DES PLAQUETTES ET LE TEMPS D'ACTIVATION PARTIELLE DE LA

THROMBOPLASTIQUE. SEUL L'ETHINYL OESTRADIOL AUGMENTE LES TRIGLYCERIDES SERIQUES ET ABAISSE LH DANS LE SERUM
LO : CNRS-15569

13/13 PASCAL - (C) CNRS
NO : PASCAL 73-361-13640
ET : METABOLIC EFFECTS OF **OESTROGENS** TREATMENT IN PATIENTS WITH CARCINOMA OF PROSTATE: A COMPARISON OF STILBOESTROL AND **CONJUGATED** **EQUINE** **OESTROGENS**
AU : SHAHMANESH M; BOLTON CH; PENTLEY RCL; HARTOG M
AF : UNIV. DEP. MED., BRISTOL
DT : PERIODIQUE;LA
SO : BRIT. MED. J.; G.B.; DA. 1973; VOL. 2; NO 5865; PP. 512-514; BIBL. 20REF.
LA : ENG
CC : 361B04E
FD : HORMONE STEROIDE SEXUELLE; OESTROGENE; CANCER PROSTATE; STILBOESTROL; EQUILINE; EQUILENINE; METABOLISME LIPIDE; METABOLISME GLUCIDE; TRAITEMENT; HORMONOTHERAPIE; COMPLICATION TRAITEMENT; APPLICATION THERAPEUTIQUE; INDICATION; SOUS L'EFFET DE
FC : ENDOCRINOLOGIE
EG : ENDOCRINOLOGY
SG : ENDOCRINOLOGIA
LO : CNRS-5002